Supporting Information for

REVIEW

Nanomedicine for acute respiratory distress syndrome: The latest application, targeting strategy, and rational design

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Received 21 January 2021; received in revised form 23 March 2021; accepted 6 April 2021

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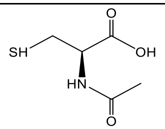
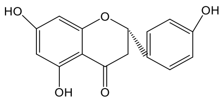
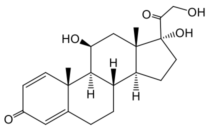
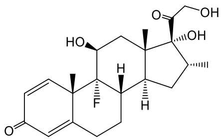
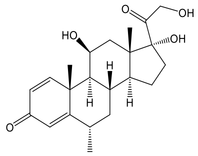
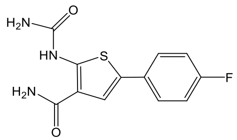
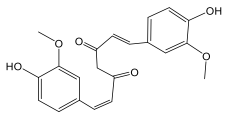
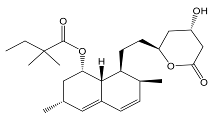
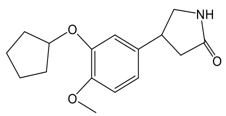
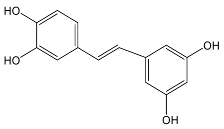
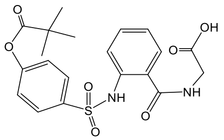
Table S1 Basic properties of drugs in nanocarriers for ARDS treatment.

Drug	Structure	pK_a	Pharmacological activity	Carrier	Encapsulation efficiency (%)	Drug loading (%)	Ref.
NAC		3.25±0.10	Antioxidants	Cationic liposomes	79.26±3.34	–	52
				PLGA NPs	–	–	53
Naringenin		7.52±0.40	Inhibition of p38 MAPK phosphorylation and oxidative stress	DPPC phytosomes	92.1±1.87	30.69±0.62	54
Prednisolone		12.46±0.70	Glucocorticoid	Polymer micelles	–	–	55
Dexamethasone		12.13±0.70	Glucocorticoid	NLC	81.39–90.11	3.28–3.62	56
				BSA NPs	84.3±2.3	6.7±0.32	57
				Liposomes	92.0±3.0	–	58
				Lysozyme dextran nanogels	–	5	59

				Monocyte membrane derived vesicles	–	40.9 ± 0.7	60
Methylprednisolone		12.46 ± 0.70	Glucocorticoid	cRGD-peptide grafted liposomes	64.8	–	61
				Liposomes	92.5 ± 0.5	–	28
TPCA-1		13.12 ± 0.50	Selective inhibitor of IκB kinase-2	Polymer micelles	85–60	10.0–24.0	27
				BSA NPs	–	25.0 ± 1.3	62
				Platelet-derived EVs	10.6	4.6	63
Curcumin		8.11 ± 0.46	Suppresses the activation of NF-κB	R7L10 peptide formed micelles	–	–	29
				PEG-PLGA microspheres	68–63.5	3.24–8.14	64
Simvastatin		13.49 ± 0.40	Anti-inflammatory and endothelium-protection	NLC	96.78 ± 0.12	4.85 ± 0.01	65
				NLC	–	–	66
Rolipram		16.02 ± 0.40	PDE4 inhibitor,	Phosphatiosomes	> 90	–	25

			suppresses the activation of neutrophil	Nanoemulsion	>95	–	67
Piceatannol		9.30 ±0.10	Reduced neutrophil infiltration and inhibit the NF-*κ*B pathway	BSA NPs	10–14	–	68
				Neutrophils-derived vesicles	–	1.7	69
Sivelestat		3.67 ±0.10	Inhibitor of neutrophil elastase	Interbilayer-crosslinked multilamellar vesicles	60 ±5	–	70
DNase-I	Endonuclease	–	Alleviate NETosis dysregulation	PLGA NPs	–	–	71
				Melanin-like nanospheres	–	–	72
siRNA	–	–	Mediate gene silencing and inhibit the	Phosphorus-based dendrimer	–	–	73
				Guanidinated and	–	–	74

		expression of pro-inflammatory cytokines	fluorinated bifunctional helical polypeptides			
			Pulmonary surfactant coated nanogels	–	–	75

–, not applicable; BSA, bovine serum albumin; cRGD, cyclic arginine glycine-D-aspartic acid; DPPC, dipalmitoylphosphatidylcholine; EVs, extracellular vesicles; MAPK, mitogen activated protein kinase; NAC, *N*-acetylcysteine; NF-*κ*B, nuclear factor-*κ*B; NPs, nanoparticles; PLGA, poly(lactic-*co*-glycolic acid).

Table S2 Pulmonary delivery of nanomedicine for ARDS therapy.

Platform	Drug	Size (nm)	Charge (mV)	Animal model	Therapeutic schedule	Note	Ref.
PLGA NPs	NAC	197.5	−10.4	*i.p.*, LPS, rat	*i.t.*, 2 h before injury	Improved the delivery of antioxidant and inhibited inflammation	53
	EpoR cDNA	196	−20.63	Hyperoxic lung injury, rat	Inhalation, one week after injury	Achieved rapidly uptake by lung epithelial cells and sustained release of EpoR cDNA, attenuated apoptosis and oxidative stress	100
	Plasmid HO-1 and LPS binding peptide	~170	+36.2	*i.t.*, LPS, mice	*i.t.*, immediately after injury	Reduced the expression of HO-1 and proinflammatory cytokines	30
PAM NPs	Dexamethasone and adiponectin gene	57.05	+16.59	*i.t.*, LPS, mice	*i.t.*, immediately after injury	Achieved higher efficiency in delivering adiponectin gene	96
Polydopamine NPs	-	~80	-	*i.n.*, LPS, mice	*i.n.*, 0.5 h after injury	Eliminated ROS and suppressed neutrophils	79

Fluorinated α-helical polyplexes	siRNA	~150	~10	*i.t.*, LPS, mice	*i.t.*, 2 h after injury	Potentiated mucus and cell membrane penetration	74
Hydrophilic polymer nanogels	–	~55	−2	*i.t.*, LPS, mice	*i.t.*, after injury	Hydrophilic nanogels inhibited LPS induced immune response	106
Pulmonary surfactant coated nanogels	siRNA	~125	~−30	*i.t.*, LPS, mice	*i.t.*, 24 h before injury	SP-B enhanced cytosolic delivery of siRNA and internalization by resident alveolar macrophages	75
Nanoemulsions	Dimethyl silicone	69.2	–	*i.t.*, HCl, rat	*i.t.*, after injury	With defoaming effect and inhibited pulmonary edema	107
PAM-Chol polymer micelles	HO-1 gene and resveratrol	120.4	+40.9	*i.t.*, LPS, mice	*i.t.*, 2 h after injury	Improved transfection efficiency and inhibited NF-κB	99
PS-PEG polymer nanomicelles	–	47.3	–	*i.t.*, HCl, mice	*i.t.*, 5 h after injury	Synthetic polymers for replacing pulmonary surfactant	108
Phosphorus-based dendrimers	siRNA	120–190	30–50	*i.n.*, LPS, mice	*i.n.*, 24 h before injury	Pyrrolidinium modified dendrimers formed complexation with siRNA and enhanced cellular uptake	73

cRGD-peptide grafted liposomes	Methylprednisolone	156	−24.2	*i.t.*, IL-1β, rat	Inhalation, 0.5 h before injury	Blocked interactions of neutrophil-ECM and inhibited pro-inflammatory mediators	61
Cationic liposomes	NAC, vitamin C and E	138.5	+34.5	CLP-rat	*i.t.*, dairy, 5 d after injury	Restoration of redox balance	52
DPPC phytosome	Naringenin	150.8	+20.97	*i.t.*, HCl, rat	*i.t.*, 10 min after injury	Improved the bioavailability of antioxidant and inhibited MAPK pathways	54
SP-C antibody conjugated lipoplexes	miR-486	~215	~−5	Mice	*i.n.*	SP-C antibody conjugated for specific targeting to lung AEC II	109
DPPC-DOPE nanovesicles	–	200−300	–	*i.t.*, HCl, mice	Inhalation, 5 min after injury	Pulmonary surfactant aerosols, endocytosed by AEC II and improved pulmonary functions	110
Peptide self-assembled NPs	Src tyrosine kinase inhibitor	~700	–	*i.t.*, LPS, mice	*i.t.*, 1 h before injury	Improved the biocompatibility	83

R3V6 peptide formed micelles	S1PLyase siRNA and recombinant HMGB-1 box A peptide	~50	–	*i.t.*, mice	LPS, *i.t.*, 2 h after injury	Combinational therapy for siRNA delivery and anti-inflammation	31
R7L10 peptide formed micelles	Curcumin and plasmid DNA	~100	–	*i.t.*, mice	LPS, *i.t.*, 2 h after injury	Improved efficiency of plasmid DNA and curcumin	29
EPCs derived exosomes	miRNA-126	30−120	–	*i.t.*, mice	LPS, *i.t.*, 4 h after injury	Target to regulate HMGB-1 and VCAM-1 expression for reducing lung inflammation and dysfunction	111
Au NPs	–	13	−36.4	*i.t.*, mice	LPS, *i.t.*, 2 h before injury	Targeted pulmonary macrophages and inhibited TLR signals	112
	–	~13	–	*i.t.*, mice	LPS, *i.t.*, 2 h before injury	Inhibition on neutrophil and regulation of Tregs	113
	–	19.7	–	*i.n.*, mice	LPS, *i.t.*, 1 h before injury	Inhibition on TLR4 signaling pathways	114
	–	13.3	–	*i.n.*, mice	LPS, *i.t.*, 1 h before injury	Inhibited TLR4 and induced autophagy	115

Porous $Se@SiO_2$ nanospheres	–	55	~−19	*i.n.*, mice	LPS,	*i.n.*, 1 h before injury	Targeted mitochondria to improve airway epithelial cells	116

–, not applicable; AEC II , alveolar type II epithelial cells; CLP, cecal ligation and puncture; cRGD, cyclic arginine glycine-D-aspartic acid; DOPE, phosphatidylethanolamine; DPPC, dipalmitoylphosphatidylcholine; ECM, extracellular matrix; EPCs, endothelial progenitor cells; EpoR, erythropoietin receptor; HCl, hydrochloric acid; HMGB-1, high mobility box-1; HO-1, heme oxygenase-1; *i.n.*, intranasal; *i.p.*, intraperitoneal; *i.t.*, intratracheal; IL, interleukin; LPS, lipopolysaccharide; MAPK, mitogen activated protein kinase; NAC, *N*-acetylcysteine; NF-*κ*B, transcription factor nuclear factor-*κ*B; NPs, nanoparticles; PAM, polyamidoamine; PLGA, poly (lactic-*co*-glycolic acid); PS-PEG, poly(styrene-*b*-ethylene glycol); ROS, reactive oxygen species; S1PLyase, sphingosine-1-phosphate lyase; SP, surfactant protein; TLR, Toll-like receptor; VCAM-1, vascular cell adhesion molecule-1.